PATENT
File No.: 98-60C1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Zeren Gao et al.
Serial No.	:	09/541,752
Filed	:	March 31, 2001
For	:	ANTIBODIES TO GROWTH FACTOR HOMOLOG ZVEGF3
Examiner	:	Spector, L.
Art Unit	:	1647
Docket No.	:	98-60C1
Date	:	July 7, 2003

Commissioner for Patents
P.O. Box P.O. Box 1450
Alexandria, VA 22313-1450

Declaration of Christopher Clegg Under 37 C.F.R. § 1.132

Sir:

I, Christopher Clegg, do hereby declare as follows:

1. I am currently employed by ZymoGenetics, Inc., the assignee of the above-named patent application, as Research Director, Immunology.

2. I received a Ph.D. in Zoology from the University of Washington in 1984.

3. I have read the Office Action mailed March 14, 2003 in the above-identified patent application ("the Patent Application"), including the rejections under 35 U.S.C. §§ 102(e) and 103(a). I am providing this Declaration to assist the patent examiner in evaluating the teachings of Ferrara et al., U.S. Patent No. 6,391,311.

4. Claims 33-36 of the Patent Application recite an antibody that specifically binds to an epitope of a polypeptide consisting of a sequence of amino acid residues as shown in SEQ ID NO:2 from residue 235 to residue 345. SEQ ID NO:2 is

the sequence of a human protein referred to in the Patent Application as "zvegf3." This protein is now more commonly known as "PDGF-C" and is described, for example, by Li et al. (Nature Cell Biol. 2:302-309, 2000). Residues 235 and 345 of PDGF-C are the approximate boundaries of the active growth factor domain of the protein.

5. PDGF-C is secreted as an inactive precursor that requires specific proteolytic cleavage for activation. This cleavage separates the growth factor domain from the remainder of the molecule, which comprises an amino-terminal CUB domain and an interdomain region. The structure and proteolytic activation of PDGF-C are described in the Patent Application, for example at pages 18-20 and 118-120. This requirement for proteolytic activation was subsequently confirmed by others, including Li et al. (ibid.).

6. In view of PDGF-C's requirement for proteolytic activition, it is likely that the active region (i.e., the growth factor domain) is buried within the full-length, precursor form of the protein and becomes exposed only after cleavage between the interdomain region and the growth factor domain. Thus, if the full-length protein were injected into an animal for the purpose of raising antibodies, one could not predict, with a reasonable liklihood of success, that an antibody that specifically binds to an epitope within the growth factor domain would be obtained. Even if a small portion of the CUB domain or the interdomain region was removed, the remaining amino-terminal residues would be expected to mask the active region.

7. I therefore conclude that if an animal was immunized with a polypeptide comprising at least about 80% of the PDGF-C ("VEGF-E") sequence disclosed by Ferrara et al., one skilled in the art would not reasonably expect to obtain an antibody that specifically binds to an epitope of a polypeptide consisting of a sequence of amino acid residues as shown in SEQ ID NO:2 of the Patent Application from residue 235 to residue 345.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that the making of willfully false statements and the like is punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and may jeopardize the validity of any patent issuing from this patent application.

July 7, 2003
Date

Christopher Clegg